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Conference Report

DMCCB Basel Symposium on 'Targeting RNA by Small Molecules'

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The DMCCB Basel symposium organized by the Division of Medicinal Chemistry and Chemical Biology (DMCCB) of the Swiss Chemical Society (SCS) focused on 'Targeting RNA by Small Molecules' and took place in a virtual format on the February 4, 2021. The topic of the conference was selected by vote of the members of the medicinal chemistry and chemical biology division (DMCCB). The audience was comprised of participants from industry and academia from all over the world and out of the 150 attendees, around half were students. Six keynote speakers showed the importance of developing new methods to target RNA and how this can be done in versatile ways.

The conference opened with an inspiring presentation by ***Dr. Kamal Azzaoui***, CEO and co-founder of Saverna Therapeutics focusing on developing RNA-targeting small molecule drugs to combat diseases with unmet medical needs, such as Lupus Erythematosus. Dr. Azzaoui gave insights into the most recent research projects and how the company applies machine learning to optimize hit identification and lead optimization. Already in this first talk it became clear that RNA has the potential for a huge new target space in drug discovery. Saverna's approach for drug discovery involves fragment-based screening by NMR.[1] The data on fragment binding, or lack of binding, to the target pre-miRNA, is used to identify compounds which can be purchased and analyzed for selectivity as well as in cellular and biochemical assays.[2]

The second enlightening presentation, tackling the function of cytosine-5 RNA methylation in translation, was given by ***Prof. Michaela Frye*** from the Deutsches Krebsforschungszentrum (DKFZ). To start the talk, Prof. Frye highlighted the importance of chemical modifications in RNA and pointed out that this knowledge has been around for decades. However, the tools to detect them were lacking. Her laboratory focuses on the exploration of the cytosine-5 RNA methylation which is required for normal development and aberrant RNA methylation which can lead to severe human diseases. To dissect the roles of RNA methyltransferases and their methylated target RNAs in normal development, human diseases and cancer, her lab uses a combination of novel transcriptome-wide quantitative analyses and well-established mouse and human *in vitro* and *in vivo* differentiation models.[3,4]

The second part of the symposium started with the talk of ***Dr. Oliver Rausch*** from Storm Therapeutics. Their research focuses on the discovery and development of small molecules modulating RNA epigenetics.[5,6] The company is particularly interested in the inhibition of m6A methyltransferase METTL3 which is a novel target for acute myeloid leukemia (AML), using ligand activity mapping and SAMalogue library. After the development of a first potent and selective small molecule compound for METTL3, the screening was later extended to different chemical series. Initially, Dr. Rausch used different panels of cell lines from which the most sensitive ones were those of pancreatic, ovarian, lung and hematologic origins. Later, *in vivo* testing was performed which demonstrated efficacy in AML models as well as inhibition of lung cancer xenograft growth. Mass spectrometry was used to confirm the engagement of METTL3 in cell lines and *in vivo* and multiple pharmacodynamic biomarkers were used to demonstrate METTL3 inhibition in these models. With this strong preclinical data in hand, STC-15 has been selected for first stage clinical trials as the first-in-class drug candidate targeting METTL3.

The second speaker of the afternoon section was ***Prof. Amanda E. Hargrove*** from Duke University whose research focuses on the identification of new scaffolds to target RNA.[7] The approach of her group is to analyze patterns in RNA-biased small molecule chemical space, and RNA topological space prone to differentiation. This strategy was applied to functionally modulate conformations of triple helix in the long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). As a successful example of this exciting work, Dr. Hangrove presented a library of compounds containing the key diphenylfuran moiety which was designed and synthesized to test the affinity, stability, and the selectivity for MALAT1 enzymatic degradation *in vitro*. In the second part of her presentation, she presented results of an RNA-focused small library for binding to the enterovirus EV71, that show specificity to the bulge, which is confirmed by nuclear magnetic resonance spectroscopy and isothermal calorimetry.[8] She concluded with her current work on targeting regulatory RNA in SARS-CoV-2 by using an RNA-biased amiloride scaffold.

After the afternoon break, the third and last industrial speaker, ***Dr. Iris Alroy*** from Anima Biotech, explained how Anima's platform technology could lead to new small molecules targeting the regulation of mRNA translation machinery. This innovative technology led to the identification of highly specific hits with local visualization of mRNA translation. Remarkably, this allows a tissue specific visualization due to a differential regulation for a same mRNA depending on the tissue, which is incredibly powerful in novel drugs discovery context. The company's technology was illustrated with three examples. The first one was the modulation of Collagen type I (COL1A1) translation to treat lung fibrosis, leading to highly selective compounds in lung fibroblasts. The second was the discovery of compounds that selectively reduce c-Myc, a proto-oncogen overexpressed in many cancers, by changing c-Myc mRNA processing leading to the formation of RNA granules, preventing translation. Finally, the last example presented the selective regulation of mRNA coming from mutated mHTT gene in Huntington's disease.[9]

In the closing presentation, ***Prof. Matthew D. Disney*** from Scripps Research Institute Florida discussed the results of sequence-based design of small molecules targeting RNA using a high throughput library-versus-library screening approach in a two-dimensional combinatorial screening setup. This approach, named Inforna, can identify druggable RNA motifs, and so disease-causing RNAs containing these motifs, as well as the selective hits which bind them. Once the target and the drug compound binding-site are known, further investigations lead to the elimination of these RNA by using for example targeted degradation, which recruits nucleases while binding RNA druggable-pocket. Two research projects from Prof. Disney team were presented. The first described the discovery of small molecules targeting RNA repeat expansion, such as r(CUG)^{exp} involved in Fuchs' endothelial corneal dystrophy (FECD) and type-1 myotonic dystrophy (DM1).[10,11] In this case, designed monomeric degraders especially bind to r(CUG)^{exp} located in an intron and not in an untranslated region, and trigger its degradation mediated by nuclear RNA exosome. As a second example, the same method led to the design of Ribonuclease Targeting Chimeras (RIBOTACs) targeting the precursor to oncogenic microRNA-21, which is upregulated in triple-negative breast cancer and causes metastasis.[12] The designed RIBOTACs recruit RNase L which cleaves pre-miRNA-21. Overall, these brilliant examples demonstrate that sequence-based design approach can be used to quickly obtain highly selective and potent small molecules targeting RNA.

To close the DMCCB Symposium 2021, the winner of the poster award was announced. The prize was won by ***Dr. Alexandre Hofer*** from the University of Cambridge for his poster presentation 'Selective chemical functionalization of N6-methyladenosine in DNA'.[13] Dr. Hofer will receive financial support for the admission to a scientific conference of his choice.

The online DMCBB Basel symposium 2021 gathered more than 150 attendees from industry and academia. We deeply thank the organizing committee, the Swiss Chemical Society, as well as the corporate sponsors for inviting wonderful speakers and for making this event a great success during these challenging times.

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